Remarks

Claims 23, 34, 45, 54, 63 and 64 have been amended to further define the claimed embodiments as discussed below. These amendments are supported by the specification and claims as originally filed. In particular, claims 63 and 64 were amended to correct obvious typographical errors. Support for the amendment to claims 23, 34, 45, and 54 is found, for example, in paragraph [0090]. Thus, no new matter has been added.

Claims 1-45 and 48-64 will be pending upon entry of this amendment.

I. Election/Restrictions

The Examiner has indicated that the restriction has been withdrawn between Groups I and II.

II. Specification

The Examiner has noted the use of trademarks in the application and has requested capitalization of each trademark and that each be accompanied by the generic terminology. Applicants acknowledge Examiner's comments and have reviewed the application in order to ensure that the marks are not used in a manner "which might adversely affect their validity as trademarks." No amendments to the specification are believed to be necessary.

III. Rejections Under 35 U.S.C. § 101 and 112, First Paragraph

The Examiner has rejected claims 1-45 and 48-64 under 35 U.S.C. § 101 as allegedly not supported by either a substantial asserted utility or a well established utility. Specifically, the Examiner alleges that the "assertion that the disclosed protein has biological activities similar to known NK-3 related proteins is not credible in the absence of supporting evidence..." and that the "specification does not support a credible, specific and substantial utility regarding the claimed polypeptides for purposes unrelated to the asserted biological activity." The Examiner has further rejected claims 1-45 and 48-64 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention, based on the supposed lack of a specific and substantial credible utility.

a. Asserted Utilities are Specific

As disclosed in the specification and discussed by the Examiner, NKX3.1 is homologous to a number of homeodomain-containing transcription regulators. The specification teaches that the NKX3.1 polypeptide is a transcription regulator expressed particularly in prostate tissue. Further, the specification teaches that polynucleotides, polypeptides and antibodies

corresponding to NKX3.1 are useful reagents for diagnosing diseases and conditions, such as prostate cancer, associated with aberrant expression of NKX3.1. *See*, specification at paragraphs [0090]-[0107]. The specification also discloses that NKX3.1 polynucleotides, polypeptides and/or agonists (which include agonist antibodies) are useful to treat diseases associated with a decrease in the level or function of NKX3.1 including cancers, particularly prostate cancer. *See*, specification at paragraphs [0090]-[0108].

According to the Utility Examination Guidelines, the test for specificity is whether an asserted utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention, such as use of a complex machine for landfill. *See*, Utility Examination Guidelines. The disclosed utilities for NKX3.1 polypeptides discussed above are specific, in that not every protein may be used to, for example, to generate antibodies for diagnosing cancer. Consequently, the skilled artisan would most certainly not consider such a use to be a "throw-away utility" such as landfill.

According to the USPTO's published description of a specific asserted utility, the claimed polypeptides are specific because (1) they are specific for the subject matter claimed (e.g., not all polypeptides have uses in the diagnosis of cancer) and (2) the specification discloses a disease or condition which can be diagnosed (e.g., cancer).

b. Asserted Utilities are Substantial

Moreover, the disclosed utilities for NKX3.1 polypeptides discussed above are substantial, as "the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." *See*, Revised Interim Utility Guidelines Training Materials, page 6. Pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 USC § 101. *See*, Nelson v. Bowler, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980); *See also,* M.P.E.P. §2107.01(III). It is well-established that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and satisfies the utility requirement. *Id.* Accordingly, the utilities asserted by Applicants are clearly substantial.

c. Asserted Utilities are Credible

The asserted utilities have been challenged as allegedly not credible. In particular, the Examiner has taken the position that homology is not predictive of function. As a result, the Examiner concludes that "in the absence of supporting evidence" the assertion that NKX3.1 has

activity as a transcription regulator similar to known NK-3 related proteins is not credible. See, Office Action, pages 5-7.

The Examiner further alleges that the "specification does not support a credible, specific and substantial utility regarding the claimed polypeptides for purposes unrelated to the asserted biological activity." Specifically, the Examiner alleges that the specification "does not disclose any correlation between the DNA binding activity and the role of the protein in transcriptional regulation of any gene;" "does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptides;" and "does not predict whether the claimed polypeptides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control." The Examiner concludes that the "proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides."

Applicants respectfully disagree. As an initial matter, Applicants point out that "an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101." M.P.E.P. § 2107.02(III)(A); *see also*, In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). "Where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot simply dismissed as 'wrong.'" M.P.E.P. § 2107.02 (III)(B). "Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made.." M.P.E.P. § 2107.02. Further, the PTO must accept the manner of making and using an invention disclosed in a specification "unless there is a reason for one of skill in the art to question the objective truth of the statement of utility or its scope." In re Langer, 183 U.S.P.Q. at 297; *see also, In re* Marzocchi, 58 C.C.P.A. 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) *and Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1098-99 (Jan. 5, 2001). Indeed, the Federal Circuit has characterized the standard for utility by indicating:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *See Brenner v. Manson*, 383 U.S. 519, 534 (1996); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 247, 275 (7th Cir. 1903) (the test for utility is whether the invention "is capable of serving any beneficial end").

Juicy Whip, Inc. v. Orange Bang Inc., 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999).

Accordingly, the burden is on the Examiner to establish why it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, "question") the truth of the statement of utility. *See,* M.P.E.P. § 2107 at 2100-30; *In re* Brana, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995); and, *In re* Cortright, 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999). The Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. *See id.* Such a *prima facie* showing must contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not specific, substantial, and credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.* Moreover, if applicants have presented reasoning used in asserting a utility, the Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the Applicants' assertion of utility. *See id.*

Applicants respectfully suggest that none of the Examiner's assertions demonstrate why a person of ordinary skill would not believe the Applicant's assertions of utility and thus do not meet the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

First, the Examiner has taken the position that homology is not predictive of function. As a result, the Examiner concludes that "in the absence of supporting evidence" the assertion that NKX3.1 has activity as a transcription regulator similar to known NK-3 related proteins is not credible. As discussed below, Applicants assert that the Examiner's position is scientifically unfounded and does not support the conclusion that the Applicant's asserted utilities are not credible.

Next, the Examiner refers to the DNA binding assays provided in Example 7 and states that no correlation has been provided between the DNA binding activity and the role of the protein in transcriptional regulation of any gene. Applicants respectfully submit that no correlation need be provided. As provided in the specification and noted by the Examiner, the specification discloses, *inter alia*, that the claimed polypeptides have "utility of a transcription factor..." See Office Action, page 5, lines 2-5. The DNA binding data provided in Example 7 shows that the human and mouse NKX3.1 homeodomains have comparable DNA binding specificity as NK-2 homeodomains. This result is consistent with the asserted utility as a transcriptional regulator and would not cause one of ordinary skill to doubt the Applicant's asserted utility.

Finally, the Examiner asserts that the specification "does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptides;" and, relatedly, that the specification "does not predict whether the claimed polypeptides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control." Applicants respectfully assert that the Examiner is in error and refer the Examiner to paragraphs [0094] through [0107] of the specification wherein a correlation between an altered level of the claimed polypeptide and prostate cancer are disclosed. Specifically, in paragraph [0097], the specification states that, "certain tissues in mammals with prostate cancer express significantly decreased levels of the NKX3.1 protein and mRNA encoding the NKX3.1 protein when compared to a corresponding 'standard' mammal, i.e., a mammal of the same species not having the cancer."

d. Examiner's Position is Scientifically Unfounded

Applicants respectfully submit that the Examiner's argument that homology is not predictive of function is scientifically unfounded and does not support a *prima facia* case of lack of utility. Applicants note that the utility guidelines state that "[t]here is no *per se* rule regarding homology, and each application must be judged on its own merits." Utility Examination Guidelines, Federal Register Vol. 66, No. 4 (January 5, 2001) Page 1096, column 3, middle. The guidelines further require that

> when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "'[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient.'' *Fujikawa* v. *Wattanasin,* 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996).

Id., page 1096, bridging columns 2-3. Applicants submit that the Examiner has not provided evidence or sound scientific reasoning to rebut Applicants assertions of utility in the instant application. The Examiner has cited six references to show that there are "numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities." The Examiner points to examples from the (1) platelet-derived growth factor (PDGF) family of proteins, citing Tischer et al. (U.S. Patent 5,194,596) and Benjamin et al (1998, Development 125:1591-8); (2) transforming growth factor (TGF) family of proteins, citing Vukicevic et al. (1996, PNAS 93:9021-26) and Massague (1987, Cell 49:437-8); (3) PTH and PTHrP related proteins, citing Pilbeam et al., (1993, Bone 14:717-20); and (4) antagonists of vertebrate growth hormone, citing Kopchick et al. (U.S. Patent 5,350,836) in support of her

argument. *See,* Office Action, pages 5-7. Applicants respectfully assert that these references do not serve to challenge the credible assertions of utility provided in the instant specification. The skilled artisan would readily recognize that members of the PDGF protein family, TGF protein family, PTH, and antagonists of vertebrate growth hormone are unrelated to the NKX3.1 protein, and thus one of ordinary skill in the art would not dismiss Applicants' asserted utility as incredible based on this information alone. Furthermore, Applicants point out that the mere existence of an unusual family member that exhibits a disparate activity from the rest of a family does not fatally undermine the fundamental relationship between structure/sequence and activity of the family. Rather, the existence of such a family member is only a piece of the art regarding the protein family and should be weighed accordingly. More specifically, if the disparate family member would not cause the skilled artisan to doubt the relatedness of a new protein to that family the mere existence of the disparate member cannot be the basis for a rejection of utility.

In addition, the Examiner has cited seven review articles in an effort to support the conclusion that "generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." However, as discussed below, none of the seven references supports this conclusion.

The Skolnick reference (Trends in Biotech 2000, 18(1):34-39) states that "[t]he sequence-to-function approach is the most commonly used function-prediction method," describing the field as "robust", "well developed", and "powerful". See Skolnick, page 34, right column. The authors further state that "sequence based approaches to protein function prediction have proved to be very useful". Page 37, right column. The Examiner has selected a portion of the Skolnick paper relating to the prediction of protein function based on *three dimensional structure* (Box 2 of Skolnick, cited at page 6 of the Office Action). However, the cited text does not address the use of *sequence homology* to predict protein function. Proteins with homologous sequences (which may also have similar three dimensional structure) are likely to share common functional attributes due to their shared evolutionary past. However, similar three dimensional structure alone may or may not reflect a shared evolutionary past. Therefore, the Skolnick reference fails to rebut the Applicants' assertions of utility in the instant application, and actually acknowledges the importance of sequence-based functional annotations.

Bork (Genome Research 2000, 10:398-400) also acknowledges that there is "no doubt that sequence analysis is extremely powerful." Page 400, column 2. The Examiner cites Bork to support the statement that "the error rate of functional annotations is considerable" (Office Action at page 6). However, Table 1 of Bork indicates 90% accuracy in the prediction of

functional features by homology. While Bork may suggest that certain types of predictions (e.g. the prediction of human promoters) may be less accurate than others, there is nothing in the reference that challenges the credibility of the asserted uses in the instant application. Certainly the reference does not support the broad conclusion that homology is not predictive of function.

The Examiner cites Doerks and colleagues (Trends in Genetics 1998, 14:248-250) as illustrating the problems of underprediction (not identifying all of a protein's functions) and overprediction (erroneously assigning function to a protein) using annotated sequence databases. However, Doerks raises these concerns in the context of discussing large scale, computer-automated annotation of genetic data. The primary message of the paper is to stress the importance of human interaction in functional annotations. To illustrate their point, the authors were able to make functional assignments to previously "uncharacterized protein families" (UPF's) using *comparative sequence analysis*. See, e.g., page 248, column 2, under "Function prediction for the UPFs". Accordingly, the Doerks reference can not support the conclusion that homology is not predictive of function.

Smith et al. (Nature Biotechnology 1997, 15:1222-1223) have been cited for their remark that "[t]here are numerous cases in which proteins of very different current functions are homologous" on the basis of sequence similarity. Office Action at page 7, citing Smith at page 1222, column 3. This isolated statement says nothing of the credibility of the assertions made in the instant application. Moreover, when the Smith article is read as a whole, it is clear that the authors' primary concern is errors introduced by automated, large-scale sequence annotation methods. Smith notes that such automated annotation methods are based on

> successful approaches used by many researchers to assign probable functions to new sequences when previously studied and recognizable homologs exist. However, when applied in an automated manner to large data sets with minimum review, such approaches can lead to serious degradation of the wealth of incoming genomic data."

Page 1222, column 1, emphasis added. Thus, Smith and colleagues do not suggest abandoning sequence-based functional analysis, but merely caution against large scale *computer automated* functional annotation of sequence databases. Such a concern is not relevant to the instant application directed to a *single* protein identified by *human* scientists.

Brenner (Trends in Genetics 1999, 15:132-133) also voices concern about large scale, computer automated functional annotation of genetic databases. Brenner's theoretic statement that most homologs must have different molecular and cellular functions is in stark contradiction to the overwhelming evidence that the art clearly relies on functional assignments based on

sequence homology. Furthermore, there is nothing in the reference that challenges the credibility of the asserted uses described in the instant application.

Bork (Trends in Genetics 1996, 12(10):425-427) raises several concerns relating specifically to automated sequence annotation by "software robots", none of which are relevant to the instant application directed to a protein identified by *human* scientists.

Finally, Bowie and colleagues (Science 1990, 247:1306-10) are cited for their remark that "[b]ecause an amino acid sequence contains all of the information necessary to determine the structure of a protein, it should be possible to predict structure from sequence, and subsequently to infer detailed aspects of function from the structure. However, both problems are extremely complex, and it seems unlikely that either will be solved in an exact manner in the near future." Office Action at page 7, citing Bowie at page 1306, column 1, 2nd full paragraph. Applicants respectfully assert that the Bowie reference is not relevant to the instant application. The remarks are directed to instances wherein proteins with divergent sequences possess similar structure, and as a consequence, similar function. In contrast, the instant application is directed to proteins with similar sequences, and thus similar structure and function.

e. Post-filing Date Data Corroborates Asserted Utility

As discussed *supra*, Applicants assert that the Examiner has failed to meet her burden in demonstrating a lack of utility for the claimed inventions. However, even assuming that the Examiner has met her burden, Applicants direct the Examiner's attention to Steadman *et al.* (Nucleic Acids Research, 2000, 28(12):2389-95; a copy is attached herewith as Reference A97). The Steadman reference discloses that NKX3.1 specifically repressed transcription of luciferase from a report vector in an *in vitro* reporter gene assay (*See* Abstract). This corroborates Applicants assertion that NKX3.1 functions as a transcription regulator. See paragraphs [0090]-[0107]. Applicants note that the supportive evidence cited in the Steadman reference, dated after the applicants' filing date, "can be used to substantiate any doubts as to asserted utility since it pertains to the accuracy of a statement already in the specification." *See e.g., In re Brana* 51 F.3d 1560, 1567 at n19 (Fed. Cir. 1995).

Thus, Applicants have asserted that NKX3.1 has both significant identity and similar biological activity to known NK-3 related proteins and have provided Steadman et al. which corroborates this assertion. Accordingly, even assuming that the Examiner has made a prima facie showing that Applicants' asserted utility is not credible, Applicants respectfully submit that the prima facie showing has been rebutted, and that the presently claimed invention possesses credible, well-established utilities that constitute patentable utilities under 35 U.S.C. § 101.

e. Conclusion

In summary, Applicants have asserted specific, credible, and substantial uses for NKX3.1 polynucleotides, polypeptides, and antibodies. No sound scientific reasoning has been put forth to challenge the credibility of these assertions. To the contrary, it is clear that sequence homology analysis is frequently relied upon to make functional assignments to novel proteins. Thus, one of skill in the art would reasonably find the asserted utilities to be credible based on the described sequence homology to known NK-3 related proteins. Furthermore, subsequent publications have confirmed Applicants' assertions, rendering moot any questions as to their credibility. In view of the foregoing, Applicants respectfully request that the rejection of claims 1-45 and 48-64 under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

IV. Rejections Under 35 USC § 112, First Paragraph

a. Biological Deposit

The Examiner has rejected claims 12-22, 34-44 and 54-62 under 35 U.S.C. §112, first paragraph, requesting a statement that the biological material recited in claims 12-22, 34-44 and 54-62 was deposited under the terms of the Budapest Treaty, and that all restrictions upon public access to the deposit will be irrevocably removed upon granting of the patent. *See*, Office Action, pages 9-12.

In response, Applicants' representative hereby gives the following assurance by signature below.

> Human Genome Sciences, Inc., the assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209 (present address). The deposits were made on April 28, 1997, accepted by the ATCC, and given ATCC Accession Numbers 209005 and 209006. In accordance with M.P.E.P. § 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Numbers 209005 and 209006 will be irrevocably removed upon the grant of a patent based on the instant application, except as permitted under 37 C.F.R. § 1.808(b). A copy of the ATCC Deposit Receipt for Accession Numbers 209005 and 209006 is enclosed herewith as Exhibit B.

The Examiner has also requested that the specification be amended to recite the date of deposit and complete name and street address of the depository. Applicants note that the requested information already appears in the specification in paragraphs [0009] and [0022].

Therefore, Applicants respectfully request that the rejection of claims 12-22, 34-44 and 54-62 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn

b. Written Description

The Examiner has rejected claims 23-45 and 48-62 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with written description requirement. The Examiner directs this rejection to the claims involving polypeptide fragments of at least 30 or 50 amino acids of SEQ ID NO:2 or 4 (or the polypeptide encoded by the DNA of ATCC Deposits No. 209005 or 209006), and polypeptide variants having 95% amino acid sequence homology to SEQ ID NO:2 (or the polypeptide encoded by the DNA of ATCC Deposits No. 209005 or 209006). Specifically, the Examiner alleges that:

> [t]he claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity....In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved.

See Office Action, page 13, lines 1-12.

As a preliminary matter, the claims to polypeptide fragments and polypeptide variants having 95% identity to the peptides of the invention have been amended to recite that "the isolated human protein regulates transcription in prostate tissue." In view of the amendments to claims 23, 34, 45 and 54, all of the claims rejected under 35 U.S.C. §112, first paragraph are directed at least in part to fragments and/or variants of SEQ ID NO:2 or 4 (or the polypeptide encoded by the DNA of ATCC Deposits No. 209005 or 209006) which regulate transcription in prostate tissue. Therefore, the Examiner's allegation that "[t]he claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature", does not apply to the currently pending claims. See Office Action, page 13, lines 1-3.

The Examiner further asserts that "the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides [*sic*], and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation." The Examiner then states that more than a reference to a potential method of isolating a claimed compound is required, and that instead, the compound itself is required. Finally, the Examiner concludes that "only isolated polypeptides comprising the sequence set forth in SEQ ID NO:2 or 4 or amino acid residues 122-188 or 124-183 of SEQ

ID NO:2 (homeodomain region), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph."

Applicants respectfully disagree and traverse this rejection. Applicants respectfully submit that one skilled in the art could reasonably conclude that Applicants had possession of the polypeptides of the rejected claims, in the present application as filed. Applicants further submit that the Examiner has underestimated both the teaching of the present application and the level of skill in the art on the priority date of the present application.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02.

The Federal Circuit recently re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed,'" *Union Oil Company of California v. Atlantic Richfield Company*, 208 F.3d 989, 54 U.S.PQ.2d 1227 (Fed. Cir. 2000). Further, the Federal Circuit has emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification; and not whether the specific embodiments had been explicitly described or exemplified. Indeed, the court noted that "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Union Oil Company of California v. Atlantic Richfield Company*, 208 F.3d at 1001, (emphasis added).

In an analysis of written description under 35 U.S.C. § 112, first paragraph, the Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. This burden is discharged if the Examiner can present evidence or reasons why one skilled in the art would *not* reasonably conclude that Applicants possessed the subject matter as of the priority date of the present application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ2d 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04. In the instant case, the Examiner has not met this burden.

The Examiner has done nothing more than to argue a lack of literal support in alleging that the claimed invention is not described in the specification. Importantly, the Examiner has failed to provide any showing that one skilled in the art would *not* reasonably conclude that Applicants possessed the claimed subject matter as of the priority date of the present application. Accordingly, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, for lack of adequate description should be withdrawn.

Moreover, Applicants submit that the Examiner cannot meet the burden of presenting a *prima facie* case of unpatentability, because the specification describes with reasonable clarity that the inventors were in possession of the claimed invention on the priority date of the present application. The specification explicitly states, for example, in paragraphs [0068], [0071] and [0075] through [0079], that the invention includes polypeptides having at least 95% identity to SEQ ID NOs:2 or 4, and fragments (e.g., 30 and 50 amino acids in length) of the polypeptide of SEQ ID NOs:2 or 4 or the polypeptide encoded by the cDNA contained in the deposited clones.

Once one of ordinary skill in the art is enlightened by the specification and provided with, for example, the polypeptide sequences of SEQ ID NOs:2 and 4, the skilled artisan could readily envision any number of polypeptides having at least 95% identity to SEQ ID NOs:2 or 4, or polypeptide fragments comprising 30 or 50 amino acids of SEQ ID NOs:2 or 4. Furthermore, at the time of filing of the priority application, one of skill in the art would have been able to routinely test fragments and variants of the invention for ability to regulate transcription in prostate tissue using assays such as, for example, the assay described paragraphs [0112] through [0136] of the instant specification.

As taught in the specification, for example, in paragraphs [0068] through [0073], one or more amino acid residues of SEQ ID NOs:2 or 4 may be substituted with another amino acid, preferably a conservative amino acid residue. The specification also discloses regions conserved between the human and mouse NKX3.1 protein sequences (see, for example, paragraphs [0090] and [0091]). Furthermore, the amino acid alignments of human NKX3.1 with other NK proteins (shown in Figure 3A) and with mouse NKX3.1 (shown in Figure 3B) clearly indicate conserved amino acids within the NK family. The structural details described in the specification, along with the alignments shown in Figure 3, would provide the skilled artisan with ample guidance as to which amino acids could be substituted or deleted with a reasonable expectation of retaining ability to regulate transcription. Therefore, the description of the species is representative of the claimed genus and the specification clearly conveys that Applicants were in possession of the claimed invention on the priority date of the instant application. Applicants note that the level of skill in the art on the priority date of the present application was very high. Accordingly, one skilled in the art, enlightened by teachings of the present application and of the amino acid sequences of the SEQ ID NOs:2 and 4, could readily envision countless polypeptide sequences that comprise the specified polypeptides.

Thus, from reading the specification, the skilled person would immediately recognize that, at the time the specification was filed, the Applicants had "invented what is claimed" (*Vas-*

Cath, 935 F.2d at 1563). Therefore, the specification contains an adequate written description of the claimed polypeptides.

In *University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997) (hereinafter "*Eli Lilly*") the Federal Circuit held that in order to satisfy the written description requirement

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

(Emphasis added.)

Thus, the Federal Circuit indicated that the written description requirement for generic claims to genetic material, such as cDNA, may be satisfied by providing the sequences of a representative number of nucleic acids which fall within the scope of the genus or by providing a recitation of structural features common to a substantial portion of the members of the genus. Applicants assert that, to the satisfaction of the second test set forth in *Eli Lilly*, Applicant's description of the reference polypeptides SEQ ID NOs:2 and 4 provides one skilled in the art with the necessary recitation of structural features common to members of the genus, which features "constitute a substantial portion of the genus." *Id.* The recitation of the structural features of the reference protein is a recitation of the structural features common to the members of the genus because the proteins included within the genus will have 30 and 50 contiguous amino acids and/or 95% of their amino acid sequence (primary structure) in common to the reference polypeptides of SEQ ID NOs:2 or 4. As discussed above, once one of ordinary skill in the art is enlightened by the specification and provided with, for example, the reference polypeptide sequences of SEQ ID NOs:2 and 4, the skilled artisan could readily envision any number of polypeptide fragments that would comprise 30 or 50 amino acids of the reference polypeptide sequences and any number of polypeptides comprising a polypeptide sequence which is 95% identical to the polypeptide sequences of SEQ ID NOs:2 or 4. Therefore, the description of the species is representative of the claimed genus and the specification clearly conveys that Applicants were in possession of the claimed invention on the priority date of the instant application.

c. Enablement

The Examiner has rejected claims 1-45 and 48-64 under 35 U.S.C. §112, first paragraph, because the specification allegedly "does not reasonably provide enablement for making or using a full-length human (or murine) NKX3.1 protein of SEQ ID NO:2 or 4 or a full length NKX3.1 protein encoded by genomic DNA or cDNA of ATCC Deposit No. 209005 and 209006

or proteins having at least 95% identity with the protein of SEQ ID NO:2 or 4 or peptides comprising 30 or 50 contingous [sic] amino acids of SEQ ID NO:2 or 4." Specifically, the Examiner alleges that: (1) the "specification is not enabling for expressing a recombinant full length NKX3.1 protein from a host cell"; (2) the "specification is not enabling for showing a correlation between NKX3.1 mRNA and protein expression in vitro or in vivo"; and (3) the "specification is not enabling for...polypeptides having at least 95% identity with...NKX3.1, or for...fragments and derivatives of the...NKX3.1 polypeptide."

1) Expression of Full Length NKX3.1

The Examiner references Example 7 of the specification, and alleges that the example is the "only working example showing actual expression of any part of a NKX3.1 protein." The Examiner cites a passage in Example 7 of the specification wherein it is stated that murine NKX3.1 is predicted to "be poorly expressed in bacterial cells" to support her contention that the specification "teaches away from being able to even express a full-length NKX3.1 protein in a bacterium." Finally, the Examiner concludes, based upon this alleged teaching in view of the prior art and an alleged lack of working examples, that "the specification is strongly dispositive to one of ordinary skill in the art being enabled for making the NKX3.1 protein and its fragments, variants and derivatives thereof."

Applicants respectfully disagree and traverse.

To satisfy the enablement requirement, the specification must enable a person of ordinary skill in the art to practice a single use of the claimed polypeptides without undue experimentation. *See, e.g.,* MPEP §2164.01(c). To make a proper enablement rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP §2164.04; *see also, In re Wright*, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants respectfully submit that the Examiner has not provided sufficient evidence or a basis to question the enablement provided in the specification for the claimed polypeptides.

Applicants respectfully remind the Examiner that actual reduction to practice is not required. See, *In Re* Sivaramakrishnan, *673 F.2d 1383; 1982 CCPA LEXIS 166; 213 U.S.P.Q. (BNA) 441* (CCPA 1982). In fact, the filing of a patent application serves as conception and constructive reduction to practice. *See*, M.P.E.P. §2138.05 and *Hyatt v. Boone, 146 F.3d 1348, 1352, 47 USPQ2d 1128, 1130*. Further, the Court has held that written description of prophetic invention/examples is patentable so long as it enables one of ordinary skill in the art to practice

the invention without undue experimentation. See, *In Re Wands, 858 F.2d 731; 1988 U.S. App. LEXIS 13208; 8 U.S.P.Q.2D (BNA) 1400* (Fed. Cir. 1988).

Applicants respectfully submit that the Examiner has overinterpreted the teaching of the specification with respect to expression of the full-length mouse or human NKX3.1 proteins. The specification does not state that the proteins are incapable of expression in bacterial cells, only that they were predicted to "be poorly expressed in bacterial cells." See paragraph [0208], emphasis added. Thus, the specification does not teach "away from being able to even express a full-length NKX3.1 protein in a bacterium" as was asserted by the Examiner (emphasis added). In fact, at most, the language of Example 7 suggests that bacteria would not be the first choice in host cell for expressing the full-length NKX3.1 protein. Applicants respectfully direct the Examiner to paragraph [0054] of the specification, wherein a range of host cells is contemplated. The list provided includes, *inter alia*, mammalian cells and insect cells, which have not been disclosed to have an equivalent limitation in their protein expression.

Thus, the specification provides a range of suitable hosts for expression of the full-length NKX3.1 proteins of the invention. And, while the specification suggests a less than optimal expression level from bacterial cells, in no way is it implied that expression would not be possible. As discussed above, once one of ordinary skill in the art is enlightened by the specification and provided with, for example, the polypeptide sequences of SEQ ID NOs:2 and 4 and the teachings regarding optimal choice of host cells; the skilled artisan could readily express the claimed polypeptides in any number of suitable systems. Applicants submit that the expression of NKX3.1 protein and its fragments, variants and derivatives is fully enabled by the disclosure of the specification and requests that the instant rejection be reconsidered and withdrawn.

2) Correlation of mRNA to Protein Levels

The Examiner alleges that the specification does not enable the use of the claimed polypeptides because the specification does not demonstrate "an expressed full-length recombinant protein, an isolated or purified protein from a natural source or that a functional translational product for the human NKX3.1 protein can be obtained from a NKX3.1 mRNA." The Examiner further asserts that specification demonstrates "NKX3.1 mRNA expression in various tissues...without showing correlative protein expression levels."

Relatedly, it was also asserted that:

> Those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. There are many steps in the pathway leading from DNA to protein, and

> all of them can in principle be regulated. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-translational regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated.

See, Office Action dated 9/20/2006, page 17, lines 14-22.

The Examiner cites Greenbaum, *et al.* as further support for the assertion that "expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression" in order to conclude that the specification's teaching of mRNA expression does not teach protein expression and thus, in the absence of working examples, does not enable use of NKX3.1 proteins. The Examiner points to three proposed reasons for the alleged poor correlation "generally reported in the literature" between mRNA and protein levels: "complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein"; substantial variation of in vivo half-lives for proteins; and significant noise and/or error in measurements of protein and mRNA concentrations. *See* present Office Action, page 18, lines 1-20.

Applicants respectfully disagree and traverse.

Applicants point out that "it is not necessary that a patent applicant test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one of skill in the art to carry out the invention commensurate with the scope of his claims." *Chugai*, 927 F.2d at 1213 (citing *Angstadt*, 537 F.2d at 502)(emphasis added). In addition, Applicants point out that empirical data is not a threshold requirement for sufficient enabling disclosure. Instead, it has been found that "a patent specification is required to contain a disclosure, either through illustrative examples or written description, that is sufficient to teach one skilled in the art how to make and use the invention as broadly as it is claimed. *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)(emphasis added).

According to the court, "[a]s a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (emphasis added). Further, the court has found that "it is incumbent upon the Patent Office, whenever a rejection [for lack of enablement] is made, to explain why it doubts the truth or accuracy of any

statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." Cf. *In re Gazave*, 54 CCPA 1524, 379 F.2d 973, 154 USPQ 92 (1967); *In re Chilowsky*, 43 CCPA 775, 229 F.2d 457, 108 USPQ 321 (1956).

The Applicants respectfully submit that the Examiner has not met this burden. The Examiner has not provided any reason to doubt the supporting disclosure in the specification, nor has any "acceptable evidence or reasoning which is inconsistent with the contested statement" been provided. Additionally, Applicants must respectfully disagree with the conclusion that "expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression." First, although it is true that mRNA expression levels do not always exhibit a directly proportional correlation with protein expression levels, the lack of at least some general correspondence is the exception rather than the rule. Indeed, the comment in Alberts et al. was in fact worthy of publication precisely because it represents an exception to the norm, not because it is a paradigm of the norm. In fact, Alberts et al. also teaches "For most genes transcriptional controls are paramount. This makes sense because of all the possible control points...only transcriptional control ensures that no superfluous intermediates are synthesized." *See*, Alberts et al., Molecular Biology of the Cell, 3rd edition, page 403, last paragraph (1994) (Reiterated in the Summary paragraph, page 404; "Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control.") (Emphasis added).

Hence, when investigating the expression levels of a new gene and protein those of ordinary skill in the art most often look to mRNA expression levels as predictive of the relative protein expression levels. And, as corroborated by Alberts et al., most genes are, in fact, transcribed into mRNA and translated into protein in direct proportion to their relative mRNA expression levels. Indeed, Greenbaum, *et al.* states that "while mRNA expression values have shown their usefulness in a broad range of applications...these results are almost certainly only correlative, rather than causative; in the end it is most probably the concentration of proteins...that are the true causative forces in the cell." See Greenbaum, *et al.*, page 117.3, 2nd paragraph in right column (emphasis added).

Thus, Greenbaum confirms that the usefulness of mRNA expression values in "a broad range of applications" is due the correlation with "the concentration of proteins." This statement seems on its face to contradict the reference to poor correlation later in the paper. However,

Greenbaum sheds light on this contradiction in the concluding paragraphs of the paper. The authors state "we believe that a major limitation to finding correlations is the degree of natural and manufactured systematic noise in mRNA and protein expression experiments." See page 117.6, right column, 2nd paragraph (emphasis added).

The authors seem to feel that correlation of mRNA and protein expression levels happens more often than reported in large part due to technological barriers and experimental noise/errors and not due a lack of biological correlation. Greenbaum discusses attempts to describe and reduce this noise. The reference provided, reference #50 in the Greenbaum article, describes errors and corrections for microarray expression data. In fact, the main thrust of Greenbaum, *et al.* is on the large-scale (genome-wide) comparison of mRNA and protein expression data, and not on the specific testing for correlation between a single mRNA and its corresponding protein product. Thus, the conclusions drawn in Greenbaum regarding errors in large-scale, genome-wide expression testing are not directly applicable to the correlation of mRNA/protein expression in general.

The Applicants submit that one of skill in the art, at the time the application was filed, would have considered correlation between NKX3.1 mRNA levels and NKX3.1 protein levels much more likely than not. As a result, Applicants submit that the expression of NKX3.1 protein and its fragments, variants and derivatives is fully enabled by the disclosure of the specification and requests that the instant rejection be reconsidered and withdrawn.

3) Variants of 95% ID, Fragments and Derivatives

The Examiner alleges that the claims are not enabled for variants with 95% identity to the claimed sequences, fragments, and derivatives thereof. More particularly, the Examiner alleges:

> The specification does not support the broad scope of the claims which encompass all modifications to the amino acid sequence because the specification does not disclose...the general tolerance to modification;...the specific positions and regions of the sequence(s) which can be predictably modified...; and...guidance as to which of the infinite choices is likely to be successful.

(*See,* Office Action, Page 20, lines 6-13).

The Examiner concludes that "[w]ithout such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue."

Applicants respectfully disagree and traverse.

To satisfy the enablement requirement, the specification must enable a person of ordinary skill in the art to practice a single use of the claimed polypeptides without undue experimentation. *See, e.g.,* MPEP §2164.01(c). To make a proper enablement rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP §2164.04; *see also, In re Wright*, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants respectfully submit that the Examiner has not provided sufficient evidence or a basis to question the enablement provided in the specification for the claimed polypeptides.

As a preliminary matter, the claims to polypeptide fragments and polypeptide variants having 95% identity to the peptides of the invention have been amended to recite that "the isolated human protein regulates transcription in prostate tissue." In view of the amendments to claims 23, 34, 45 and 54, all of the claims rejected under 35 U.S.C. §112, first paragraph are directed at least in part to fragments and/or variants of SEQ ID NO:2 or 4 (or the polypeptide encoded by the DNA of ATCC Deposits No. 209005 or 209006) which regulate transcription in prostate tissue.

The Federal Circuit has held that *making the claimed species and screening them for function is acceptable*, as long as the experimentation is not undue. As in all cases, this is the test: whether it would require undue experimentation to practice the invention – even when a claim might encompass some inoperative embodiments. *See generally, Atlas Powder v. E.I. Du Pont de Nemours & Co.* 750 F.2d 1569, 224 U.S.P.Q. (BNA) 409 (Fed. Cir. 1984). Therefore, it is clearly not *per se* undue to make and test several fragments or variants, particularly when specific guidance was clearly disclosed in the specification coupled with what was known in the art at the time the invention was filed. The specification provides the screening assays or they were known in the art as of the filing date.

With regard to retention of the biological activity of the claimed NKX3.1 variants, the instant specification provides detailed guidance in predicting which amino acid substitutions, additions and deletions would affect the biological activity of the protein. First, the specification describes in detail several structural domains of the NKX3.1 protein (*see* Figure 4). Thus, the skilled person is given guidance as to the important structural features of the NKX3.1 protein. Second, Figure 3 provides an alignment of the human NKX3.1 protein sequence with the homologous NK proteins, to show regions of conservation and divergence. Changes in amino acids residues *outside* these regions of homology would be less likely to affect the activity of the NKX3.1 protein (*see*, for example, paragraphs [0069]-[0070]).

Furthermore, Figure 4 shows secondary structural features of the NKX3.1 protein, including alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; and surface probability. These features shown in Figure 4 would also be useful in predicting which amino acid substitutions, additions or deletions would be likely to maintain the structural conformation and electrochemical properties of the protein. By choosing alterations that maintain these structures, the activity of the protein could be maintained.

Thus, the skilled person could both screen the claimed polypeptide variants to see which retain the biological activity of NKX3.1, and design such alterations using the guidance provided in the specification and routine methods known in the art. Therefore, one skilled in the art could readily make and use the claimed polypeptides with, at most, only routine experimentation. Accordingly, Applicants request that the instant rejection under 35 U.S.C. § 112, first paragraph for alleged lack of enablement be withdrawn.

V. Rejections Under 35 USC § 102

The Examiner has rejected claim 64 under 35 USC § 102 (a) as allegedly being anticipated by Sciavolino et al. (Developmental Dynamics 209: 127-138 (May 1997) ["Sciavolino"].

Applicants respectfully traverse this rejection.

When any claim of an application is rejected under 35 USC § 102 (a) based on a printed publication which substantially shows or describes the same patentable invention, the inventor(s) of the subject matter of the rejected claim may submit a Declaration Under 37 CFR § 1.131 showing invention prior to the publication date of the printed publication to remove the publication as prior art. M.P.E.P. § 715.

Applicants submit that a reference applied against generic claims may be antedated as to such claims by an affidavit or declaration under 37 CFR § 1.131 showing completion of the invention of only a single species, within the genus, prior to the effective date of the reference. M.P.E.P. § 715.02. Thus, Applicants may antedate the reference indirectly by showing prior completion of one or more species which put them in possession of the claimed genus prior to the reference date. M.P.E.P. § 715.03. Alternatively, proof of prior completion of a species different from the reference species will be sufficient to overcome a reference indirectly under 37 CFR § 1.131 if the reference species would have been obvious in view of the species shown to have been made by the Applicants. *Id.*

Applicants Kenneth C. Carter and Wei-Wu He have previously submitted in the parent application (U.S. Appl. No 09/105,470) a Declaration Under 37 CFR § 1.131, executed by

Kenneth C. Carter, indicating that the nucleotide sequence depicted in SEQ ID NO:1 and the corresponding protein sequence depicted in SEQ ID NO:2, were in their possession in the United States before the publication date of Sciavolino.

Thus, Sciavolino is not available against the pending claims as prior art under 35 USC § 102 (a). Accordingly, the Examiner is respectfully requested to reconsider and to withdraw the rejection under 35 USC § 102 (a) over Sciavolino.

The Examiner further rejected claim 64 under 35 USC § 102 (b) as being anticipated by Bieberich et al. (J. Biol. Chem. 271:31779-31782 (December 13, 1996) ["Bieberich"].

Applicants respectfully traverse this rejection.

As a preliminary matter, Applicants assert that the Examiner has incorrectly rejected claim 64 under 35 USC § 102 (b) over Bieberich. Examiner is directed to paragraph [0001] of the specification where priority is properly claimed to U.S. Prov. Appl. No. 60/051,080 filed June 27, 1997. Thus, the cited reference was not first published greater than one year before the earliest priority date of the instant application and thus is not available as art under 35 USC § 102 (b).

As indicated *supra*, Applicants Kenneth C. Carter and Wei-Wu He have previously submitted in the parent application (U.S. Appl. No 09/105,470) a Declaration Under 37 CFR § 1.131, executed by Kenneth C. Carter, indicating that the nucleotide sequence depicted in SEQ ID NO:1 and the corresponding protein sequence depicted in SEQ ID NO:2, were in their possession in the United States before the publication date of Bieberich.

Thus, Bieberich is not available against the pending claims as prior art under 35 USC § 102 (a). Accordingly, the Examiner is respectfully requested to reconsider and to withdraw the rejection under 35 USC § 102 (a) over Bieberich.

Conclusion

Entry of the above amendment is respectfully solicited. In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the allowance of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an additional extension of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Dated: March 20, 2007

Respectfully submitted,

By _____

Melissa J. Pytel
Registration No.: 41,512
HUMAN GENOME SCIENCES, INC.
14200 Shady Grove Road
Rockville, Maryland 20850
(301) 610-5764

MJP/MJH/EC

Exhibit A

NKX2.1 full-length sequence

redacted Patent Questionaire

Fig #1

Exhibit A

```
          10                  30                  50
          .                   .                   .
ATGCTCAGGGTTCCGGAGCCGCGGCCCGGGGAGGCGAAAGCGGAGGGGGCCGCGCCGCCG
M  L  R  V  P  E  P  R  P  G  E  A  K  A  E  G  A  A  P  P

          70                  90                  110
          .                   .                   .
ACCCCGTCCAAGCCGCTCACGTCCTTCCTCATCCAGGACATCCTGCGGGACGGCGCGCAG
T  P  S  K  P  L  T  S  F  L  I  Q  D  I  L  R  D  G  A  Q

          130                 150                 170
          .                   .                   .
CGGCAAGGCGGCCGCACGAGCAGCCAGAGACAGCGCGACCCGGAGCCGGAGCCAGAGCCA
R  Q  G  G  R  T  S  S  Q  R  Q  R  D  P  E  P  E  P  E  P

          190                 210                 230
          .                   .                   .
GAGCCAGAGGGAGGACGCAGCCGCGCCGGGGCGCAGAACGACCAGCTGAGCACCGGGCCC
E  P  E  G  G  R  S  R  A  G  A  Q  N  D  Q  L  S  T  G  P

          250                 270                 290
          .                   .                   .
CGCGCCGCGCCGGAGGAGGCCGAGACGCTGGCAGAGACCGAGCCAGAAAGGCACTTGGGG
R  A  A  P  E  E  A  E  T  L  A  E  T  E  P  E  R  H  L  G

          310                 330                 350
          .                   .                   .
TCTTATCTGTTGGACTCTGAAAACACTTCAGGCGCCCTTCCAAGGCTTCCCCAAACCCCT
S  Y  L  L  D  S  E  N  T  S  G  A  L  P  R  L  P  Q  T  P

          370                 390                 410
          .                   .                   .
AAGCAGCCGCAGAAGCGCTCCCGAGCTGCCTTCTCCCACACTCAGGTGATCGAGTTGGAG
K  Q  P  Q  K  R  S  R  A  A  F  S  H  T  Q  V  I  E  L  E

          430                 450                 470
          .                   .                   .
AGGAAGTTCAGCCATCAGAAGTACCTGTCGGCCCCTGAACGGGCCCACCTGGCCAAGAAC
R  K  F  S  H  Q  K  Y  L  S  A  P  E  R  A  H  L  A  K  N

          490                 510                 530
          .                   .                   .
CTCAAGCTCACGGAGACCCAAGTGAAGATATGGTTCCAGAACAGACGCTATAAGACTAAG
L  K  L  T  E  T  Q  V  K  I  W  F  Q  N  R  R  Y  K  T  K

          550                 570                 590
          .                   .                   .
CGAAAGCAGCTCTCCTCGGAGCTGGGAGACTTGGAGAAGCACTCCTCTTTGCCGGCCCTG
R  K  Q  L  S  S  E  L  G  D  L  E  K  H  S  S  L  P  A  L

          610                 630                 650
          .                   .                   .
AAAGAGGAGGCCTTCTCCCGGGCCTCCCTGGTCTCCGTGTATAACAGCTATCCTTACTAC
K  E  E  A  F  S  R  A  S  L  V  S  V  Y  N  S  Y  P  Y  Y

          670                 690
          .                   .
CCATACCTGTACTGCGTGGGCAGCTGGAGCCCAGCTTTTGGGTAA
P  Y  L  Y  C  V  G  S  W  S  P  A  F  G  *
```

underline = homeodomain

Exhibit B

pecification at page 7, as referred to in Exhibit B

shown in Figures 1 or 2 (SEQ ID NO:2 or SEQ ID NO:4), which was determined by sequencing a cloned cDNA. The NKX3.1 protein of the present invention shares sequence homology with NK-3, NK-2 and NK-4 (Figure 3) (SEQ ID NOs:5-7). The nucleotide sequence shown in Figures 1 or 2 (SEQ ID NO:1 or SEQ ID NO:3) was obtained by sequencing the PSX-lambda-1 (NKX3.1) clone, which was deposited on April 28, 1997 at the American Type Culture Collection, Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209, and given accession number 209005. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The nucleotide sequence of the genomic clone shown in Figure 5 (SEQ ID NO:8) was obtained by sequencing the HPFCA19 clone, which was deposited on April 28, 1997 at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209, and given accession number 209006.

Nucleic Acid Molecules

Unless otherwise indicated, all nucleotide sequences determined by sequencing a DNA molecule herein were determined using an automated DNA sequencer (such as the Model 373 from Applied Biosystems, Inc.), and all amino acid sequences of polypeptides encoded by DNA molecules determined herein were predicted by translation of a DNA sequence determined as above. Therefore, as is known in the art for any DNA sequence determined by this automated approach, any nucleotide sequence determined herein may contain some errors. Nucleotide sequences determined by automation are typically at least about 90% identical, more typically at least about 95% to at least about 99.9% identical to the actual nucleotide sequence of the sequenced DNA molecule. The actual sequence can be more precisely determined by other approaches including manual DNA sequencing methods well known in the art. As is also known in the art, a single insertion or deletion in a determined nucleotide sequence compared to the actual sequence will cause a frame shift in translation of the nucleotide sequence such that the predicted amino acid sequence encoded by a determined

American Type Culture Collection

12301 Parklawn Drive • Rockville, MD 20852 USA • Telephone: 301-231-5519 or 231-5532 • FAX: 301-816-4366

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Human Genome Sciences, Inc.
Attn: Robert H. Benson
9410 Key West Avenue
Rockville, MD 20850

Deposited on Behalf of: Human Genome Sciences, Inc. (Ref. PF219)

Identification Reference by Depositor:	**ATCC Designation**
DNA Plasmid NKX3.1	209005 ✓
DNA Plasmid HPFCA19	209006 ✓

The deposits were accompanied by: __ a scientific description __a proposed taxonomic description indicated above.

The deposits were received April 28, 1997 by this International Depository Authority and have been accepted.

AT YOUR REQUEST:

X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested May 1, 1997. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

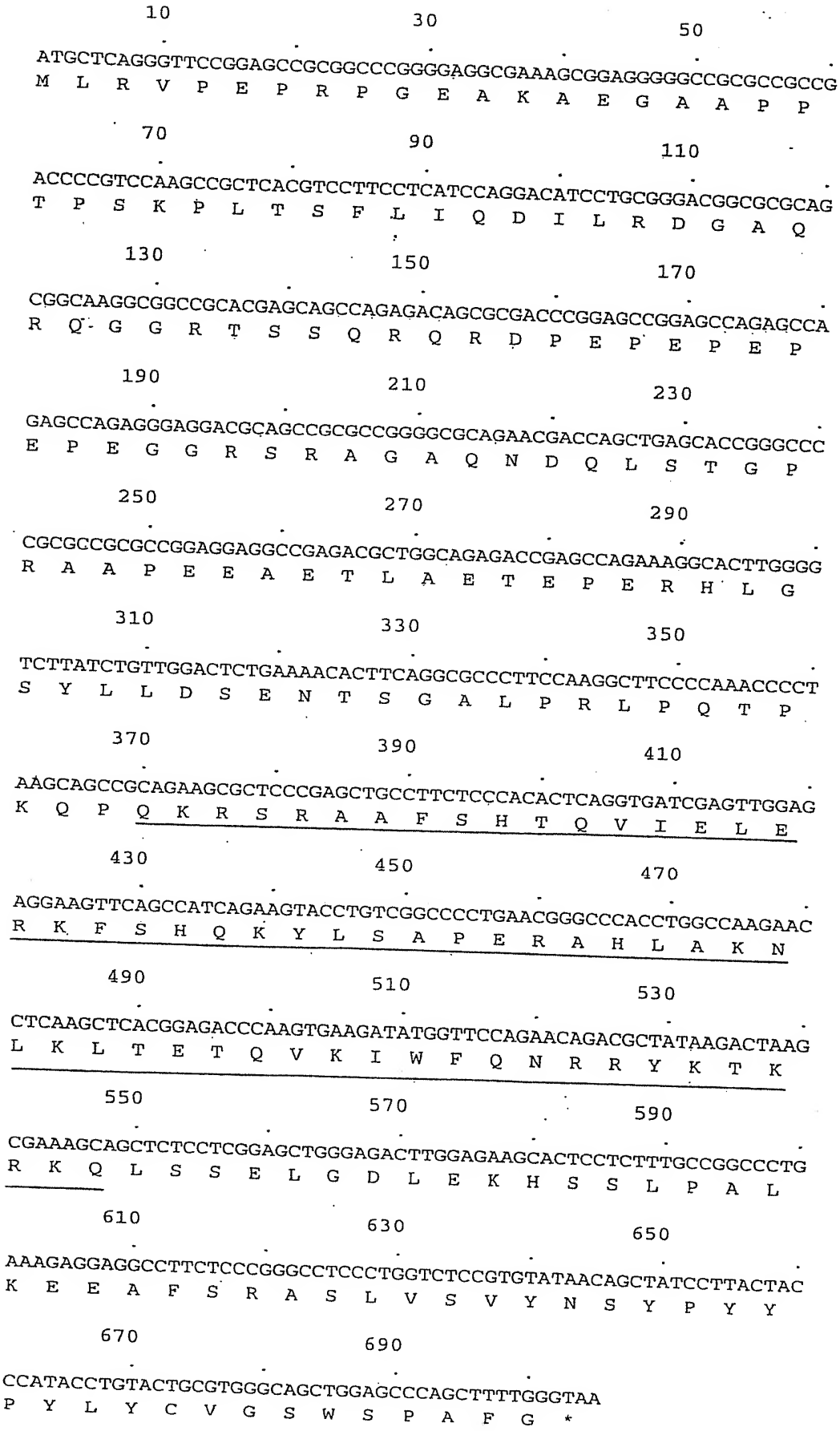
Barbara M. Hailey

Barbara M. Hailey, Administrator, Patent Depository

Date: May 1, 1997

Exhibit C

Figure 1


10
30
50
ATGCTCAGGGTTCCGGAGCCGCGGCCCGGGGAGGCGAAAGCGGAGGGGGCCGCGCCGCCG
M L R V P E P R P G E A K A E G A A P P
70
90
110
ACCCCGTCCAAGCCGCTCACGTCCTTCCTCATCCAGGACATCCTGCGGGACGGCGCGCAG
T P S K P L T S F L I Q D I L R D G A Q
130
150
170
CGGCAAGGCGGCCGCACGAGCAGCCAGAGACAGCGCGACCCGGAGCCGGAGCCAGAGCCA
R Q G G R T S S Q R Q R D P E P E P E P
190
210
230
GAGCCAGAGGGAGGACGCAGCCGCGCCGGGGCGCAGAACGACCAGCTGAGCACCGGGCCC
E P E G G R S R A G A Q N D Q L S T G P
250
270
290
CGCGCCGCGCCGGAGGAGGCCGAGACGCTGGCAGAGACCGAGCCAGAAAGGCACTTGGGG
R A A P E E A E T L A E T E P E R H L G
310
330
350
TCTTATCTGTTGGACTCTGAAAACACTTCAGGCGCCCTTCCAAGGCTTCCCCAAACCCCT
S Y L L D S E N T S G A L P R L P Q T P
370
390
410
AAGCAGCCGCAGAAGCGCTCCCGAGCTGCCTTCTCCCACACTCAGGTGATCGAGTTGGAG
K Q P Q K R S R A A F S H T Q V I E L E
430
450
470
AGGAAGTTCAGCCATCAGAAGTACCTGTCGGCCCCTGAACGGGCCCACCTGGCCAAGAAC
R K F S H Q K Y L S A P E R A H L A K N
490
510
530
CTCAAGCTCACGGAGACCCAAGTGAAGATATGGTTCCAGAACAGACGCTATAAGACTAAG
L K L T E T Q V K I W F Q N R R Y K T K
550
570
590
CGAAAGCAGCTCTCCTCGGAGCTGGGAGACTTGGAGAAGCACTCCTCTTTGCCGGCCCTG
R K Q L S S E L G D L E K H S S L P A L
610
630
650
AAAGAGGAGGCCTTCTCCCGGGCCTCCCTGGTCTCCGTGTATAACAGCTATCCTTACTAC
K E E A F S R A S L V S V Y N S Y P Y Y
670
690
CCATACCTGTACTGCGTGGGCAGCTGGAGCCCAGCTTTTGGGTAA
P Y L Y C V G S W S P A F G *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
CARTER and HE
Appl. No. 09/105,470
Filed: June 26, 1998
For: **Human NK-3 Related Prostate Specific Gene-1**

Art Unit: 1633
Examiner: Chen, S.
Atty. Docket: 1488.0790001/EKS/GLL

Declaration of Kenneth C. Carter and Wei-Wu He Under 37 C.F.R. § 1.131

Commissioner for Patents
Washington, D.C. 20231

Sir:

Each of the inventors in the captioned application, Kenneth C. Carter and Wei-Wu He, hereby declare and state that:

1. I am an inventor of subject matter described and claimed in the above-identified U.S. patent application, which is assigned to Human Genome Sciences, Inc. (HGS). The work described below occurred in the United States.

2. The above-identified patent application relates to the isolation and characterization of a cDNA encoding a novel gene product designated NK-3 Related Prostate Specific Gene-1 protein.

3. The nucleotide sequence of and the amino acid sequence encoded by cDNA clone HPFCA19, which are disclosed in the captioned application, were determined by us prior to December 14, 1996.

4. Attached hereto as Exhibit A is a copy from an HGS Patent Questionnaire with the polynucleotide sequence and the deduced amino acid sequence encoded by the cDNA clone HPFCA19. The date redacted from Exhibit A is prior to December 14, 1996.

5. The HGS Clone ID "HPFCA19" was used to identify the cDNA clone when it was deposited with the American Type Culture Collection (ATCC) on April 28, 1997, and later was assigned ATCC Deposit No. 209006 (Exhibit B). On information and belief, this deposit is described in the specification at page 7, lines 11-13.

6. The nucleotide and amino acid sequences disclosed in Exhibit A correspond to the sequences disclosed in Figure 1 of the above-identified application. A copy of Figure 1 is attached hereto as Exhibit C.

7. I declare further that all statements made in this Declaration are of my own knowledge and are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

12/12/00
Date

Kenneth C. Carter

Date

Wei-Wu He